PATENT SPECIFICATION

955,766

NO DRAWINGS

955,766

Date of Application and filing Complete Specification: June 12, 1962.
No. 22596/62.
Application made in Switzerland (No. 6979) on June 14, 1961.
Application made in Switzerland (No. 4464) on April 12, 1962.
Complete Specification Published: April 22, 1964.

Index at acceptance:—C2 C(3C5A3, 3C5C4, 3C5C7, 3C5E2); C1 B3F2
International Classification:—C 07 c (C 05 f)

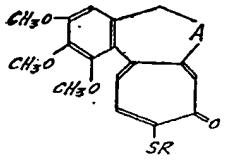
COMPLETE SPECIFICATION

New Thioethers and process for their manufacture

We, CIBA LIMITED, a body corporate organised according to the laws of Switzerland, of Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

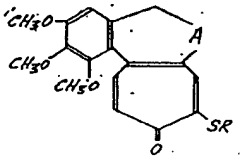
The present invention relates to new thioethers, a process for their manufacture and their use.

The present invention provides thioethers of the following formulæ



(normal series)

and



(iso-series)

in which A represents an ethylene or vinylene group and R represents an alkyl group advantageously a lower alkyl group, for example methyl, ethyl, propyl, butyl, pentyl or hexyl, and a process for preparing them.

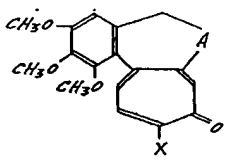
The term "lower" in qualifying the alkyl groups is used herein to mean those groups containing up to 6 carbon atoms.

The new compounds have a cytostatic and anti-mitotic effect. They inhibit cell division by preventing the formation of the spindle (metaphase) during the process of nucleus division. They can therefore be used as medicaments in human and veterinary medicine, for example for treating myeolic leucaemia, more especially subacute and chronic manifestations, and other kinds of cancerous diseases, attacks of gout and rheumatism and precancerous or cancerous conditions of the skin, for example keratoma senile, epithelium basocellulare or spinocellulare, morbus Bowen or relapses after the X-ray treatment of skin tumours. The new compounds can also be used in the cultivation of plants to produce polyploid plants. The compounds of the normal series are particularly effective, in fact considerably more so than colchicine or desacetylmethyl colchicine.

[*Price 4s. 6d.*]

The new compounds are obtained by reacting a compound of the formula

(III)



—in which X represents an etherified hydroxyl group and A has the aforesaid meaning—or the corresponding iso-compound or a mixture of these two compounds with a compound of the formula RSH or a salt thereof, R having the aforesaid meaning.

The etherified hydroxyl group is advantageously a hydroxyl group substituted by an aliphatic hydrocarbon group, for example an alkoxy group, such as the methoxy group.

The reaction may be performed in the presence of an acidic catalyst or in an alkaline medium. The reaction is preferably carried out in the presence of a solvent and/or diluent, at room temperature or below or above it,

under atmospheric or superatmospheric pressure. As an acidic catalyst there may be used a strong organic acid such, for example, as para-toluenesulphonic acid, benzenesulphonic acid or a mineral acid such as hydrochloric acid, or a Lewis acid such as zinc chloride or boron trifluoride. When the reaction is carried out in an alkaline medium, it is possible, for example, to react an alkylmercaptan in the form of a salt thereof, such as a salt of lithium, sodium or potassium, or the reaction may be performed in the presence of a strong base, such as an alkali metal hydroxide or alcoholate.

Another process for the manufacture of the new compounds in which A represents the 1:2-ethylene group consists in hydrogenating an S-alkyl-N-desacetylthiocolchiceine, which is quaternated at the nitrogen atom, and/or a corresponding iso-compound. As substituents quaternizing the nitrogen atom there may be mentioned those which are not split off from the nitrogen atom by hydrogenation, such as lower alkyl groups.

Hydrogenation is performed under conditions in which no de-sulphurization takes place and in which the tropolone ring is not attacked. It is of advantage to use hydrogen in the presence of a palladium catalyst, such as palladium on carbon. The reaction is carried out in a manner known *per se*, preferably in the presence of a solvent, for example a lower alkanol, such as ethanol, at a low or elevated temperature, but preferably at room temperature.

The thioethers are isolated in the pure form in a known manner, for example by fractional crystallization and/or adsorption, elution and crystallization. The adsorption advantageously takes the form of chromatography. From the resulting fractions the ethers are obtained in a pure form by crystallization.

The starting materials are known or can be prepared by known methods. Those compounds of the formula III in which X represents an alkoxy group, and the corresponding iso-compounds, can be prepared by the process described in British Patent Application No. 20677/62 (Serial No. 955,764) and in British Patent Application No. 20678/62 (Serial No. 955,765), by reacting des-(acetylamino)-colchiceine or Δ^6-dehydro-des-(acetylamino)-colchiceine with a diazoalkane.

The new compounds may be used as medicaments, for example in the form of pharmaceutical preparations, or may be used, for example in the form of compositions, for the cultivation of polyploid plants.

Accordingly, the present invention also provides pharmaceutical preparations which comprise the new compounds in admixture or conjunction with a pharmaceutically suitable, organic or inorganic, solid or liquid carrier. As carriers for such pharmaceutical preparations there may be mentioned, in particular, those which do not react with the new compounds and are suitable for enteral, parenteral or topical administration such, for example, as water, alkanols, gelatine, lactose, starches, stearyl alcohol, magnesium stearate, talcum, vegetable oils, benzyl alcohols, gums, propylene glycol, polyalkylene glycols, white petroleum jelly, cholesterol or other known medicinal carriers. The pharmaceutical preparations may be in the form of, for example, tablets, dragees, ointments, creams or capsules, or in a liquid form as solutions, suspensions or emulsions. They may be sterilized and/or may contain assistants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters or salts for regulating the osmotic pressure, or buffers. They may also contain other therapeutically useful substances. The pharmaceutical preparations may be used in veterinary medicine. For use in veterinary medicine, the present invention also provides an animal feed comprising the new compounds in admixture with animal fodder.

The pharmaceutical preparations for use in animal feeds advantageously contain approximately 0.001 to 0.5 mg, more especially 0.01 to 0.1 mg, of active principle per dosage unit.

The amount of carrier to be used may vary within wide limits and depends above all on the route by which the medicament is administered.

The daily dose depends on the form of administration and on the individual requirements of the patient. It is easily determined by the attending physician.

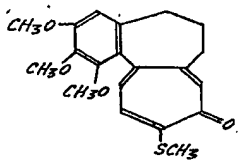
For use in the product of polyploid plants, the present invention further provides compositions comprising the new compounds in admixture or conjunction with a suitable carrier. The compositions may be, for example, in a solid form or in the form of a solution, suspension or emulsion. Suitable carriers are, for example, water, agar, glycerol or lanolin. The compositions may also contain further assistants, such as preserving, stabilizing, wetting or emulsifying agents, as well as other substances suitable for plant cultivation. Compositions in liquid form may be used, for example, for spraying plants, while in the form of ointments they can be applied to the plant as they are. Alternatively, the plant may be brushed, for example, with a solution containing the active principle, or it may be dipped into such a solution. The dose and the time for which the composition is allowed to act depend on the method of its application and on the type of plant to be treated. Since the toxicity towards plants is in general lower than that towards humans and animals, correspondingly higher doses may be applied.

The following Examples illustrate the invention.

Example 1

A mixture of 3.42 grams of des-(acetylamino)-colchicine, 1 gram of para-toluenesul-

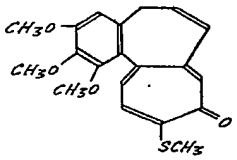
phonic acid monohydrate and 30 grams of methylmercaptan is sealed in a tube at a low temperature. The reaction mixture is kept for 6 to 12 days at 20°C and occasionally agitated. The excess methylmercaptan is then allowed to evaporate, and the residue is dissolved in ethyl acetate, water is added, and the mixture is neutralized with sodium bicarbonate; the layers are dried and the organic phase is washed with water, dried, evaporated, and the residue is crystallized from methylene chloride + ether, to yield des-(acetylamino)-thiocolchicine of the formula



melting at 164—165°C.

EXAMPLE 2

A mixture of 3.4 grams of Δ^6-dehydro-des-(acetylamino)-colchicine, 1 gram of para-toluenesulphonic acid monohydrate and 30 grams of methylmercaptan is kept for 8 days at room temperature as described in Example 1, and then worked up as described in that Example. Recrystallization from methylene chloride + ether yields des-(acetylamino)-Δ^6-dehydro-thiocolchicine of the formula



melting at 184—186°C.

EXAMPLE 3

8.79 Grams of N-dimethyl-N-desacetyl-thiocochicine iodomethylate dissolved in 2 litres of ethanol are subjected to hydrogenation for 8¼ hours under normal pressure in the presence of 3.5 grams of palladium carbon catalyst of 10% strength. The solution is freed from the catalyst and evaporated. The residue is treated with 100 cc of benzene and heated for a short time. The resulting benzene solution is separated from any undissolved constituents and evaporated. The benzene extract is chromatographed on 460 grams of aluminium oxide (activity II). By elution with 400 cc of benzene + methylene chloride 1:1 and 2500 cc of benzene + methylene chloride 1:2 there is obtained des-(acetylamino)-thio-colchicine. After recrystallization from a mixture of methylene chloride and petroleum ether the product melts at 164—165°C and is in every respect identical with the product described in Example 1.

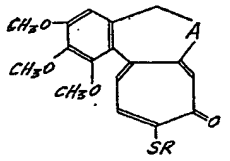
EXAMPLE 4

Tablets containing des-(acetylamino)-thio-colchicine as active ingredient can be prepared in the usual manner from:

	mg
Des-(acetylamino)-thiocolchicine	0.1
lactose	70.9
gelatine	1.5
wheat starch	35
arrowroot	12
magnesium stearate	0.2
talcum	5.3
	125.0 mg

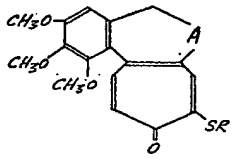
WHAT WE CLAIM IS:—

1. A compound of the formula



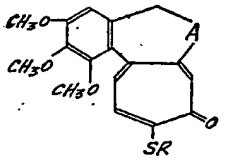
in which R represents an alkyl group and A represents an ethylene or vinylene group.

2. A compound of the formula



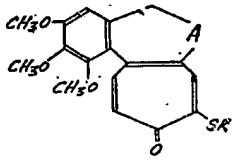
in which R represents an alkyl group and A represents an ethylene or vinylene group.

3. A compound of the formula



in which R represents a lower alkyl group and A represents an ethylene or vinylene group.

4. A compound of the formula



in which R represents a lower alkyl group and A represents an ethylene or vinylene group.

5. Des-(acetylamino)-thio-colchicine.

6. Δ^6 - Dehydro - des - (acetylamino)-thiocolchicine.

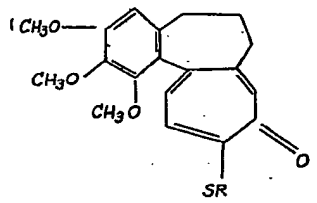
7. A pharmaceutical preparation which comprises a compound as claimed in any one of claims 1 to 4 in admixture or conjunction with a pharmaceutically suitable carrier.

8. A pharmaceutical preparation which comprises the compound claimed in claim 5 or 6 in admixture or conjunction with a pharmaceutically suitable carrier.

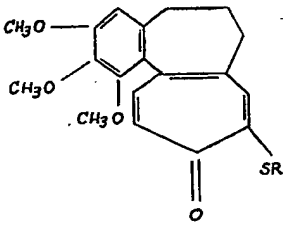
9. A pharmaceutical preparation having the composition substantially as described in Example 4 herein.

10. A composition for treating plants, which comprises a compound as claimed in any one of claims 1 to 6 in admixture or conjunction with a suitable carrier.

11. An animal feed which comprises a compound as claimed in any one of claims 1 to 6 in admixture with animal fodder.



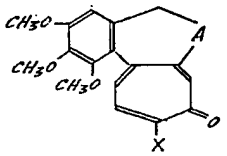
and/or



in which R has the meaning given in any one of claims 1 to 4, wherein an S-alkyl-N-desacetyl-thiocolchiceine, which is quaternated at the nitrogen atom, and/or a corresponding iso-compound is hydrogenated.

14. A process for the manufacture of a thioether conducted substantially as described in Example 1 or 2 herein.

12. A process for the manufacture of a compound as claimed in any one of claims 1 to 6, wherein a compound of the formula



in which A represents an ethylene or vinylene group and X represents an etherified hydroxyl group, or the corresponding iso-compound or a mixture of these two compounds is reacted with a compound of the formula RSH, in which R represents an alkyl group or a salt thereof.

13. A process for the manufacture of a thioether of the formula

15. A process for the manufacture of a thioether conducted substantially as described in Example 3 herein.

ABEL & IMRAY,
Chartered Patent Agents,
Quality House, Quality Court,
Chancery Lane, London, W.C. 2.

Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press (Leamington) Ltd.—1964. Published by The Patent Office, 25 Southampton Buildings. London, W.C.2, from which copies may be obtained.